

July 20, 2007

The Honorable Joe Barton
The Honorable John Shimkus
Subcommittee on Environment and Hazardous Materials
Committee on Energy and Commerce
U.S. House of Representatives
2125 Rayburn Office Building
Washington, DC 20515-6115

Dear Mr. Barton and Mr. Shimkus,

I am writing in response to the questions that you addressed to me subsequent to my presentation and responses to questions at the subcommittee's hearing on "Perchlorate: Health and Environmental Impacts of Unregulated Exposure" on April 25, 2007.

I shall first repeat your questions, and then offer my replies.

1. "You testified that people with hypothyroidism should compensate for potential perchlorate exposures through greater dietary intake of iodine rich foods and vitamins. This was also the recommendation of the "National Academy's Committee to Assess the Health Implications of Perchlorate Ingestion." Could you please talk about why you consider this so important? Please also detail what medicinal therapies or protocols are used to treat iodine deficiency, how widely available these are, what their costs are, and whether such treatments can be undergone when a woman is pregnant or breastfeeding."

Reply. Perchlorate competitively blocks the uptake of iodide by the thyroid by inhibiting the action of the sodium-iodide symporter (transporter) that carries iodine into the thyroid gland, which is the first step in thyroid hormone (thyroxine and triiodothyronine) production. Perchlorate is therefore an antithyroid drug. If the dose of perchlorate is high, little iodide enters the thyroid, and therefore thyroid hormone production falls. Increasing dietary iodide intake overcomes the inhibitory effect of perchlorate, so that the thyroid takes up more iodide and thyroid hormone production does not fall. Given this competitive interaction between iodide and

perchlorate, the effect of perchlorate can be minimized and even overcome completely by an increase in iodide intake. In short, the greater the intake of iodide, the less the effect of perchlorate.

While increasing iodide intake prevents the effect of perchlorate on the thyroid, the National Academy's Committee to Assess the Health Implications of Perchlorate Exposure (hereafter referred to as the NAS Perchlorate Committee) went beyond the issue of perchlorate to note that the iodine intake in the U.S. population as a whole decreased by approximately 50 percent between 1971-1974 (urinary iodide 310 $\mu\text{g/L}$) and 1988-1994 (urinary iodide 145 $\mu\text{g/L}$). In 1988-1994 12 percent of adults, 15 percent of women of childbearing age, and 7 percent of pregnant women had values urinary iodide values $<50 \mu\text{g/L}$, which is the World Health Organization's definition of moderate iodide deficiency (Hollowell JG, et al. Iodide nutrition in the United States. Trends and public health implications: iodine excretion data from the National Health and Nutrition Examination Surveys I and III (1971-1974 and 1988-1994). *J Clin Endocrinol Metab* 1998;83:3401-8). The results of a survey in 2001-2002 were similar to those of the 1988-1994 survey (Caldwell KL, et al. Urinary iodine concentrations: United States National Health and Nutrition Survey 2001-2002. *Thyroid* 2005;15:692-9). The reasons for this decrease include less use of salt (and therefore less use of iodized salt) and less use of iodide in processed foods, baking, and animal husbandry. These results led the NAS Perchlorate Committee to recommend that steps be taken to increase iodide intake in all pregnant women, and in particular that all prenatal vitamin preparations contain iodide. When the NAS Perchlorate Committee completed its review in 2005, approximately 50 percent of prenatal vitamins did not contain iodide, and a quick survey of two drug stores recently revealed that many prenatal vitamin products remained iodide-free.

Several national organizations recommend that pregnant women and nursing women consume more iodide than anyone else (for example, the Food and Nutrition Council of the National Research Council recommends an intake of 150 μg daily for adults, 220 μg daily for pregnant women, and 290 μg daily for nursing mothers). Iodide intake can be increased by adding iodide to all multiple vitamin products, by increasing the iodide content of salt, by encouraging or mandating that iodized salt be used in food processing and baking, and by mandating that all salt be iodinated (as is done in many countries). For bottle-fed infants, iodide intake can be increased by increasing the iodide content of infant formulas (most contain less iodine than breast milk).

The cost of these steps is very small (pennies or less per day), and the entire population would benefit. Iodide tablets are available, primarily in areas near nuclear power plants, to be ingested in the event of an explosion that releases radioactive iodine, but the doses are much higher than needed to reverse iodide deficiency. Among foods, those richest in iodide are seafood, eggs, and dairy products.

2. "You starting talking about therapies for thyroid damage, but due to time constraints were not allowed to finish your answer. Could you please expound on the points you wanted to make about thyroid damage, treatment or replacement, and the effects of perchlorate."

Reply. Iodide deficiency, compounds such as perchlorate that inhibit thyroid iodide uptake, and compounds that block other steps in thyroid hormone production (some drugs and some foods consumed in other countries) may result in a decrease in thyroid hormone production. Very small decreases in thyroid hormone production lead to an increase in secretion of thyroid-stimulating hormone (TSH, thyrotropin) from the pituitary gland, which in turn increases thyroid iodide uptake and thyroid hormone production and causes thyroid enlargement. None of these exposures or the compensatory changes cause structural damage to the thyroid, and therefore they are reversible, with two exceptions. One, thyroid enlargement, if very long-standing, may persist. Two, decreased thyroid hormone production during fetal and early postnatal life results in permanent abnormalities in neural and physical development.

Chronic thyroid disease, for example that caused by chronic inflammation (Hashimoto's disease) or radioactive iodide therapy for hyperthyroidism, is usually permanent, and therefore is treated with thyroxine. The fall in thyroid hormone production in these people elicits a similar increase in TSH secretion. This may slow the decline in thyroid hormone production, but does not usually reverse it, in contrast to the effect of TSH to restore thyroid hormone production to normal in people with a fundamentally normal thyroid gland, including those with iodide deficiency or exposed to very high doses of perchlorate.

People with chronic thyroid disease would probably be more sensitive to the antithyroid action of perchlorate than normal people, because their thyroid gland is less sensitive to the increase in TSH secretion. However, I know of no studies in which people with chronic thyroid disease were given perchlorate.

3. "Were there any other human health related topics concerning perchlorate effects or exposures that were discussed or alluded to during the hearing that you believe need to be addressed or clarified? Are there any comments that you would like to make or questions you would like to more fully answer which you did not get a chance to due to time constraints at the hearing?"

Reply. The only known effect of perchlorate is to inhibit competitively thyroid uptake of iodide. The sodium-iodide symporters that facilitate iodide uptake by the thyroid are present in other tissues, including mammary tissue and the placenta, but the extent to which the symporters in these two tissues transport iodide and whether perchlorate inhibits iodide transport into these tissues is uncertain. In one study, high breast-milk concentrations of perchlorate were not associated with low breast-milk concentrations of iodide, suggesting that perchlorate and iodide transfer into milk are unrelated (Pearce EN, et al. Breast milk iodine and perchlorate concentrations in lactating Boston-area women. J Clin Endocrinol Metab 2007;92:1673-7). Perchlorate has no effect on the function of any other organ.

There are two topics that I would like to discuss further. One is the possible effect of perchlorate in pregnant women, fetuses, and infants, and the other is the topic of pituitary-thyroid compensation for perchlorate (see below).

4. "There is much discussion about perchlorate's health effects on pregnant women, fetuses, and young children. When the National Academy's Committee to Assess the

Health Implications of Perchlorate Ingestion was reviewing existing studies on human perchlorate exposures, did you consider work on neo-natal health and breast-feeding impacts from perchlorate? Was any of the information you evaluated compelling in showing an increase in hyperthyroidism?"

Reply. The frequency of hypothyroidism in infants born in regions of high or low water content of perchlorate in the western United States varied little in most but not all studies (see Health implications of perchlorate ingestion. National Research Council. Washington, DC 2005:91-105).

More comprehensive data are available from two studies in three cities in Chile, Taltal (natural water content of perchlorate 100-120 µg/L), Chanaral (5-7 µg/L), and Antofagasta (not detectable). Among newborn infants, the only cases of hypothyroidism were in infants born in Antofagasta. Among children aged 6 to 8 years in the three cities, serum thyroid hormone and TSH concentrations and the frequency of thyroid enlargement were similar (Crump C, et al. Does perchlorate in drinking water affect thyroid function in newborns or school-age children? J Occup Environ Med 2000;42:603-12).

In a second study of pregnant women and their newborn infants in these cities, there were no consistent differences in thyroid function in the mothers during pregnancy or after delivery or in their newborn infants (Tellez RT, et al. Long-term environmental exposure to perchlorate through drinking water and thyroid function during pregnancy and the neonatal period. Thyroid 2005;15:963-75). Breast-milk iodide concentrations were not lower in the women living in Taltal, despite higher breast-milk perchlorate concentrations.

These results, taken together, provide no evidence to support the possibility that substantial quantities of perchlorate have deleterious thyroid effects (hypothyroidism) in pregnant women, their fetuses, and newborn infants. I know of no studies in which thyroid function was measured in infants being nursed for weeks or months by mothers in whom perchlorate intake and breast-milk perchlorate concentrations were high.

5. "The CDC/Blount study showed an "association" between urinary perchlorate and increased TSH and decreased total T₄ in women 12 and older, who had urine iodine levels <100 µg/L. It is possible people might assume then that perchlorate actually "caused" the thyroid changes. Was the CDC/Blount study designed to evaluate whether there is a causal relationship between low levels of perchlorate exposure and thyroid function? Can you please clarify how you view the difference between an association and causation?"

Reply. Some people will assume that the results of the CDC/Blount study (Blount BC, et al. Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States. Environ Health Perspect 2006;114:1865-71) indicate that a high perchlorate intake reduces thyroid secretion and raises TSH secretion in women with a relatively low iodide intake. That assumption is incorrect. The results indicate there may be an association between low iodide intake and high perchlorate intake and abnormal thyroid function, but they do not indicate causation (if perchlorate intake is high and if iodide intake is low, and then if thyroid secretion [serum thyroxine] falls, then serum TSH may rise — a lot of

“ifs”). To evaluate causation one must conduct a prospective study to determine if there is time dependence between these variables, and ideally a prospective study in which the key variable is a prolonged increase in perchlorate intake and iodide intake is constant. I think there are some other problems with this study. The authors do not tell us why they subdivided the subjects into two groups with urinary iodide values $<100 \mu\text{g/L}$ and $\geq 100 \mu\text{g/L}$. Was this cut-off value planned in advance or only after the authors had looked at other cut-off values for urinary iodide or some cut-off values for urinary perchlorate? The authors present predicted (not actual) changes in serum thyroxine and TSH values according to urinary perchlorate values (highest $100 \mu\text{g/L}$) in the women with urinary iodide values $<100 \mu\text{g/L}$. These predictions also presume causation, but in fact they are estimates based on statistical analyses of cross-sectional data, not prospective data. Lastly, it is important to note that the calculated decreases in serum thyroxine and increases in serum TSH values at the higher urinary perchlorate values would still be within the normal range for those measurements.

In addition to the Chilean studies, in which the perchlorate exposures were life-long, there have been five prospective studies in which known quantities of perchlorate were given to small numbers of normal adults. In the longest study (6 months) with a high dose of perchlorate (0.04 mg/kilogram per day; urine perchlorate $2000 \mu\text{g}$ daily), there was no effect on thyroid uptake of iodide or serum thyroid hormone and TSH values measured repeatedly during the study (Braverman LE, et al. Effects of six months of daily low-dose perchlorate exposure on thyroid function in healthy volunteers. *J Clin Endocrinol Metab* 2006;91:2721-4).

The NAS Perchlorate Committee chose a no-effect dose of 0.007 mg/kilogram body weight per day because that dose did not inhibit thyroid uptake of iodide when given for 2 weeks (Greer M, et al. Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans. *Environ Health Perspect* 2002;110:927-37). The committee then added an uncertainty factor of 10 to take into account the possibility that some people (pregnant women, fetuses, infants) might be more sensitive to the antithyroid action of perchlorate.

6. “As a medical doctor, specializing in thyroid function, what do you make of the split in the CDC/Blount study findings between perchlorate’s iodine effects on men and women?”

Reply. Urinary iodide values are usually from 50 to as much as 100 percent higher in men than women, indicating that men ingest considerably more iodide. What iodide-containing foods or beverages account for this difference is not known. That being the case, and given that perchlorate is a competitive inhibitor of iodide uptake into the thyroid, the same amount of perchlorate might be expected to have a greater effect on thyroid function in women. However, this has not been documented in any of the prospective studies of perchlorate administration, and the CDC/Blount paper does not give urinary perchlorate values for men.

To generalize, nearly all thyroid disorders are more common in women than men, although why women are more vulnerable is not known. A lower dietary intake of iodide may contribute to their vulnerability, but it is unlikely to explain much of the difference.

7. "Your testimony talks about the compensatory nature of the thyroid. Do you agree with this statement published by the National Academy's Committee to Assess the Health Implications of Perchlorate Ingestion: "inhibition of iodide uptake by the thyroid is duration-dependent, the effect should decrease rather than increase with time, because compensation would increase the activity of the sodium-iodide symporter and therefore increase iodide transport into the thyroid"?"

Reply. I definitely do agree with the statement. I would add that other mechanisms contribute to compensation for thyroid deficiency (including that resulting from iodide deficiency and perchlorate excess). One that is particularly relevant to iodide deficiency, as noted above, is the increase in the activity of sodium-iodide symporters in the thyroid, an increase that is not dependent on an increase in TSH secretion. A second is an increase in TSH secretion, which occurs after very small decreases in thyroid hormone production, and which alone may result in full compensation in people with many thyroid disorders. A third is an increase in the conversion of thyroxine to triiodothyronine in many extrathyroidal tissues, including the brain, which is beneficial because triiodothyronine is more potent than thyroxine.

All of these compensatory mechanisms are duration-dependent, in that they are activated by a fall in thyroid iodide uptake or in some other step(s) of thyroid hormone production. Thus, thyroid hormone production will return toward if not to normal with time, rather than decrease more.

With particular respect to perchlorate, if a daily dose is not sufficient to inhibit thyroid uptake of iodide in a few weeks, it never will, and therefore there will be no need for compensation.

I hope that my answers to your questions are clear. Please don't hesitate to let me know if they are not, or if you have additional questions.

Thank you.

Sincerely yours,

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